

Pharmacokinetics and haematological effects of desmopressin*

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Summary. The pharmacokinetics and haematological effects of 1-deamino-8-D-arginine vasopressin (desmopressin, DDAVP) after intravenous, subcutaneous and intranasal administration has been studied in man. Using a sensitive, specific radioimmunoassay for DDAVP, the AUC was determined for each route of administration. It was not significantly different for the i.v. and s.c. routes. There was no effect of the route on the plasma half-life of DDAVP which ranged from 2.7 to 4.6 h. Absorption of DDAVP after intranasal (i.n.) administration was poor. Based on AUC data, bioavailability via the two s.c. methods and the i.n. route was 112%, 94% and 2%, respectively.

DDAVP has a pronounced effect on coagulation and fibrinolytic parameters, causing a 4.0- (i.v.), 2.9- (s.c.), 3.1- (s.c.; 40 µg/ml) and 1.2- (i.n.) fold increase in factor VIII: Ag. The corresponding effect on tissue-type plasminogen activator (t-PA) was 1.9- (i.v.), 1.3- (s.c.), 2.2- (s.c.; 40 µg/ml) and 1.0- (i.n.) increase over the basal value. There was also a 1.4- to 1.6-fold increase in leukocyte count 4 h after s.c. and i.v. DDAVP. At plasma DDAVP levels greater than 300 pg/ml no correlation was found between the AUC and the maximum plasma DDAVP and biological response, which indicates a ceiling limit for exogenous stimulation of the coagulation and fibrinolytic systems.

Key words: DDAVP, desmopressin; pharmacokinetics, coagulation system, fibrinolytic system, granulocytes

D-arginine vasopressin (DDAVP, desmopressin), became the drug of choice for the treatment of central diabetes insipidus (Vavra et al., 1968). The parent molecule, vasopressin, was changed in two positions: removal of the N-terminal amino-group and substitution of L-arginine by D-arginine, which led to a significantly prolonged duration of the antidiuretic activity and a reduced pressor effect.

Like vasopressin, DDAVP has significant haematological effects and causes release of Factor VIII (FVIII) and the von Willebrand factor (vWF), as well as an increase in fibrinolytic activity (Gader et al. 1973; Cash et al. 1974; Mannucci et al. 1975, 1976). These properties of DDAVP were superior to vasopressin on a molecular level and Mannucci et al. (1977a) were the first to demonstrate the therapeutic value of DDAVP in the treatment and prevention of bleeding complications in patients with mild forms of haemophilia A and von Willebrand's disease. The agent became of further value as an important alternative to plasma-derived substitution therapy in an effort to avoid viral transmission associated with the transfusion of blood products. In addition, DDAVP has been used successfully in a number of other indications, including liver disease, uraemic bleeding and to reduce blood loss in haemostatically normal subjects undergoing open heart surgery (for review see Mannucci, 1986). Three different routes of administration have been utilized for the treatment of bleeding disorders: i.v. infusion (Mannucci 1977a), s.c. injection (Köhler et al. 1984) and i.n. (intranasal) administration (Kobayashi 1979). However, surprisingly little information is available about the pharmacokinetics of DDAVP by these routes and in conventional doses, and the relationship between the plasma level of DDAVP and the haematological response.

In 1967, Zaoral et al. synthesized a number of vasopressin analogues, one of which 1-desamino-8-

* Dedicated to Prof. Dr. P.G.Scheurlen on the occasion of his 65th birthday

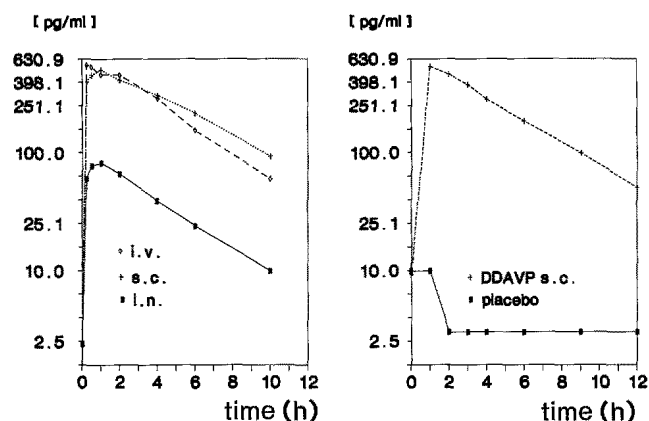


Fig. 1. Mean DDAVP level after different preparations and routes of administration. The *right side* of the graph shows the DDAVP concentration after 0.4 µg/kg of the 40 µg/ml DDAVP preparation (dashed line, cross signs) and after injection of placebo (solid line, rectangles).

The *left part* shows DDAVP concentrations after 300 µg DDAVP i.n. (solid line, rectangles) and after 0.4 µg DDAVP/kg injected s.c. (pointed line, cross signs) or infused i.v. (dashed line, diamonds) using the 4 µg/ml preparation

Table 1. Pharmacokinetics of DDAVP after i.v., s.c., and i.n. administration to 10 healthy volunteers. $M \pm SD$; coefficient of variation in parentheses

Dose and route of administration	AUC (pg·h/ml ⁻¹)	C_{max}^b (pg·ml ⁻¹)	t_{max}^c (min)	half-life (h)
0.4 µg/kg i.v.	3109 ± 1056 (34%)			3.62 ± 0.42 (12%)
0.4 µg/kg s.c. (4 µg/ml ampoule)	3492 ± 659 (19%)	568 ± 203 (36%)	87 ± 66 (76%)	3.50 ± 0.39 (11%)
0.4 µg/kg s.c. (40 µg/ml ampoule)	3164 ± 393 (12%)	544 ± 46 (8%)	60 ± 7 (12%)	3.17 ± 0.33 (10%)
300 µg i.n.	483 ± 225 ^a (47%)	98 ± 48 ^a (49%)	54 ± 39 (72%)	3.62 ± 0.42 (12%)

^a Significant difference ($p < 0.001$) compared to i.v. and s.c. routes of administration; ^b maximum concentration; ^c time to maximum concentration

Materials and methods

Experimental Design

After giving informed consent, 10 healthy male volunteers (aged 27–48 years) were each given in randomized sequence a single dose of 300 µg DDAVP by i.n. administration and 0.4 µg/kg DDAVP by i.v. infusion and s.c. injection, each dose, being separated by at least one week. Intranasal DDAVP was given with a single dose pipette (Minirinette, Ferring, Kiel, FRG) containing 0.2 ml of DDAVP sol-

ution of 1.5 mg/ml. The nasal drops were slowly applied to both nostrils with the subject sitting. Intravenous DDAVP (DDAVP 4 µg/ml, Minirin, Ferring, Kiel) was given in 100 ml saline and was infused over 30 min. Subcutaneous injection of the same preparation required a volume of up to 9 ml fluid, which was given by two injections into an extensor site in the upper arm.

In a second study, s.c. injection of a preparation containing DDAVP 40 µg/ml (Ferring, Malmö) or placebo was given to 10 other healthy volunteers (aged 22 to 33 years), in a randomized double-blind design. Informed consent according to was obtained from each subject. Each trial started at 8 a.m. after a rest period of 30 min.

Blood Collection and Assay Methods

Blood samples were collected by venepuncture prior to and 1, 2, 3, 4, 6, 9, 12 h after the end of administration. In the first study, blood were also obtained 15 min, 30 min and 24 h after the administration of DDAVP. DDAVP was assayed using a sensitive, specific radioimmunoassay, as described by Harris et al. (1986). The intra- and inter-assay coefficients of variation were 18% and 8.1%.

The laboratory methods used to measure parameters of the coagulation and the fibrinolytic system have been described in detail elsewhere (Köhler et al. 1986). t-PA was measured using an enzyme-immunoassay from BioPool, Umea, Sweden.

Data Analysis and Statistical Methods

Plasma levels of DDAVP were normally distributed and were expressed as mean \pm standard deviation (SD). The elimination half-life of DDAVP in plasma was determined by least squares regression after logarithmic transformation. In addition, the area under the plasma DDAVP-time curve (AUC) was determined, using the trapezoidal rule from the plasma DDAVP concentration versus time curve. Analysis of variance and Student's paired and unpaired *t*-test, were used for comparison.

The fibrinolytic and coagulation data were not always normally distributed. These results were expressed as median and ranges and compared using the Kruskal-Wallis and Scheffe-tests. The correlation between the maximal DDAVP levels or AUC and the maximal haematological effects (FVIII, t-PA, etc.) was calculated using the ratio of peak level to basal level. The minimum criterion for statistical significance was $p < 0.05$.

Table 2. FVIII: Ag (U/ml) after DDAVP. Median and range in parentheses. There was no significant difference between i.n. DDAVP and placebo or s.c. and i.v. DDAVP. The FVIII: Ag 60 min and 120 min after i.v. and s.c. DDAVP significantly higher was than in the placebo or i.n. groups ($p < 0.00001$)

Time	i.v.	s.c.	i.n.	Placebo	s.c. (40 µg/ml)
Prior to	0.9 (0.7–1.2)	1.2 (0.6–2.2)	1.0 (0.7–1.6)	0.8 (0.5–1.9)	1.0 (0.5–2.8)
15 min	3.0 (1.6–4.5)	1.6 (1.0–3.6)	1.0 (0.7–2.3)	ND	ND
30 min	3.3 (2.6–5.0)	2.9 (1.8–4.3)	1.1 (0.7–2.1)	ND	ND
60 min	3.6 (2.7–6.0)	3.5 (2.4–5.9)	1.2 (0.6–1.6)	0.9 (0.5–1.8)	2.9 (1.2–6.4)
120 min	3.1 (2.4–6.0)	3.1 (2.1–6.2)	1.0 (0.7–2.1)	0.9 (0.9–1.9)	3.1 (1.6–5.4)
240 min	2.5 (1.2–4.4)	2.7 (1.7–4.2)	1.2 (0.6–2.7)	0.9 (0.5–1.8)	2.4 (1.2–4.2)

ND = not determined

Results

Pharmacokinetics of DDAVP

Plasma levels of DDAVP after i.v., s.c. and i.n. administration are shown in Fig. 1. The plasma profiles indicate that elimination of DDAVP from plasma followed first order kinetics. The pharmacokinetic data are summarized in Table 1. Placebo injection gave no measurable level of DDAVP in plasma. There was no significant difference in AUC between i.v. and either method of s.c. dosing. There was no significant difference between the methods of s.c. administration in the maximum plasma concentration of DDAVP or the time to maximum concentration, although there was less variability after injection of the more concentrated DDAVP preparation. There was no effect of the route of administration on plasma elimination half-life of DDAVP, which ranged from 2.7 to 4.6 h. The absorption of DDAVP after i.n. administration of nasal drops was poor, with high interindividual variation. Based on the AUC data, the bioavailability of the s.c. route relative to i.v. administration was 112% and 94% for the low and high concentrations, respectively (not significant). In contrast, bioavailability by the intranasal route was 2%.

Haematological Effects

After i.v. infusion of DDAVP, FVIII:Ag immediately increased and reached a peak 4.0-times its initial value 60 min after the end of the infusion.

Table 3. T-PA-Antigen (ng/ml) after DDAVP. Median and range in parentheses. There was no significant difference between i.n. DDAVP and placebo or s.c. and i.v. DDAVP. The t-PA 60 min and 120 min after i.v. and s.c. DDAVP was significantly higher than in the placebo or i.n. groups ($p < 0.05$)

Time	i.v.	s.c.	i.n.	Placebo	s.c. (40 µg/ml)
Prior to	5.8 (3.3– 8.3)	7.8 (2.0–11.6)	6.6 (2.3– 8.3)	6.2 (2.2–12.0)	7.2 (1.6–11.3)
15 min	11.2 (3.4–15.4)	8.2 (2.0–12.5)	6.0 (1.4–10.8)	ND	ND
30 min	10.5 (5.1–14.5)	9.4 (1.8–13.8)	6.1 (1.4–12.8)	ND	ND
60 min	9.7 (5.3–14.8)	9.2 (3.0–14.8)	6.6 (1.4–12.8)	5.6 (1.7–16.5)	15.6 (1.7–17.0)
120 min	8.5 (2.5– 8.1)	10.4 (5.3–14.5)	5.4 (0.8–12.5)	6.0 (1.4–14.6)	11.0 (1.7–17)
240 min	5.7 (2.5– 8.1)	5.6 (1.1–10.2)	4.2 (0.8– 8.8)	6.2 (1.7–13.0)	6.8 (1.4–16.1)

ND = not determined

Table 4. Leukocyte count ($\times 10^9/l$) after DDAVP. Median and range in parentheses. There was no significant difference between i.n. DDAVP and placebo or s.c. and i.v. DDAVP. The leukocyte count 4 h after i.v. and s.c. DDAVP significantly higher than in the placebo or i.n. groups ($p < 0.00001$)

Time	i.v.	s.c.	i.n.	Placebo	s.c. (40 µg/ml)
Before	6.0 (4.2– 9.5)	7.3 (4.7–10.2)	7.3 (5.0– 9.3)	7.2 (4.4–9.4)	7.4 (4.4–11.8)
2 h	ND	ND	ND	6.3 (3.8–9.2)	6.7 (5.0–11.0)
4 h	11.0 (7.4–14.3)	10.1 (7.9–13.7)	6.4 (5.3– 8.2)	7.1 (4.4–9.1)	10.7 (9.1–14.5)
24 h	7.2 (4.8–10.8)	6.5 (4.7–11.0)	7.1 (5.0–10.2)	ND	ND

ND = not determined

After s.c. injection, FVIII:Ag increased 2.9- and 3.1-fold, while after i.n. administration only a 1.2-fold increase in FVIII:Ag was observed (Table 2). The median t-PA antigen levels at the different time intervals are shown in Table 3. An immediate, 1.9-fold increase above baseline was observed after i.v. infusion. After s.c. injection, peak levels of $1.3 \times$ (low concentration preparation, $p < 0.05$) and $2.2 \times$ the initial value ($p < 0.05$) were found 1 or 2 h after injection. Four h after s.c. or i.v. DDAVP, an increase in the leukocyte count (granulocytes) was observed. As can be seen in Table 4, the increase was not present 2 h after DDAVP, and 24 h after administration the leukocyte count had returned to the basal level. The individual increase, independent of the time interval, in FVIII:Ag and t-PA antigen is shown in Table 5. Great variation in response was observed,

Table 5. Individual increase expressed as a multiple of baseline in FVIII: Ag and t-PA (in parentheses) after DDAVP. There was no significant difference between i.v. and s.c. DDAVP, but there was between i.n. and i.v. (s.c.) DDAVP (FVIII: Ag $p < 0.001$; t-PA $p < 0.02$).

Body weight	Blood group	i.v.	s.c.	i.n.
59	A	2.9 (1.9)	4.6 (1.2)	1.1 (1.2)
61	0	5.3 (1.7)	2.5 (1.1)	1.3 (1.0)
64	0	4.6 (1.9)	4.4 (3.9)	1.6 (1.0)
66	A	3.7 (5.3)	4.3 (2.6)	1.6 (1.0)
70	0	5.0 (2.9)	3.7 (1.5)	1.0 (1.0)
74	0	4.2 (2.6)	3.6 (1.5)	1.4 (1.8)
79	0	5.5 (1.7)	5.7 (2.2)	1.0 (1.0)
82	A	2.5 (1.8)	5.7 (1.6)	1.6 (2.7)
85	0	3.4 (2.6)	2.5 (3.0)	1.2 (1.0)
92	A	3.1 (1.7)	2.3 (1.5)	1.2 (1.0)
Median		4.4 (1.8)	4.0 (1.5)	1.3 (1.0)

but the subjects could not be separated into "low" and "high" responders. No influence of blood group or body weight (after i.n. administration) on FVIII:Ag or t-PA antigen responses was apparent.

When all three routes of administration were considered, there appeared to be a significant linear correlation between maximal DDAVP-concentrations (and AUC) and the increase in leukocyte count, t-PA, FVIII: C, FVIII:Ag, vWF:Ag and ristocetin cofactor. However, when the data after s.c. injection and i.v. infusion only were considered (i.e. DDAVP-levels greater than 300 pg/ml), no significant correlation was found.

Discussion

The effects of DDAVP are manifold and include an influence on blood pressure, diuresis, an increase in vWF, FVIII and t-PA, as well as an increase in granulocytes. It is still not known whether these effects are exerted directly by DDAVP or by mediator(s) in vivo (reviewed by Mannucci, 1986). Vasodilatation, FVIII/vWF and t-PA release occur within the first hour after administration, while the increase in granulocytes was a late effect after high doses of DDAVP. A significant increase in granulocytes was observed 4 h after 0.4 µg/kg i.v. and s.c. DDAVP, resembling the effect of cortisone (Cream 1968). Thus, it seems likely that the increase in granulocytes after DDAVP is mediated by an increase in cortisone, although, unlike other analogues of vasopressin, an increase in cortisone levels was not observed after 16 µg DDAVP (equivalent to approximately DDAVP 0.2 µg/kg) by Andersson et al. (1972).

Desmopressin can be administered by i.v. infusion, s.c. injection, intranasally, sublingually and

orally (Grossman et al. 1980; Hammer and Vilhardt 1985). However, only the i.v., s.c. and i.n. routes have been shown to elicit a response in FVIII/vWF. Mannucci et al. (1981) studied the dose-response effect of i.v. administration on the increase in the FVIII/vWF. A dose of 0.3 µg/kg exerted a maximal effect on haemostasis and there was no further elevation in FVIII/vWF was on raising the dose to 0.4 µg/kg. These findings are supported by the present study in that the maximal increase in FVIII/vWF was independent of DDAVP concentrations, when it exceeded 300 pg/ml. From the data of Sørensen et al. (1984), who infused 0.2 µg/kg DDAVP, and the present results, it can be expected, that 0.3 µg/kg DDAVP would result in peak DDAVP levels ranging from approximately 400–500 pg/ml. In addition, Mannucci et al. (1981) found no significant difference in the dose range of 2 to 4 µg/kg DDAVP i.n., and the increase was 16% of that produced by i.v. DDAVP 0.3 µg/kg. The data shown here are in agreement with those results. They can be explained by the wide variation in DDAVP level after a single dose of 300 µg DDAVP (approximately 4 µg/kg), which ranged from 28 to 183 pg/ml. Harris et al. (1986) recently demonstrated that intranasal administration of DDAVP by spray resulted in a peak DDAVP level of 675 ± 528 pg/ml, which produced an almost 4-fold increase in FVIII:C. It appears, therefore, that new intranasal formulations of DDAVP may also be employed in the treatment of bleeding disorders, although the lesser variability of DDAVP level still favours the use of the s.c. or i.v. route, when a maximal, reliable effect on the haemostatic system is essential.

No additional factors, which may influence the biological response to DDAVP, are known. At least in patients with haemophilia, intraindividual variation is thought to be minimal, in spite of the considerable interindividual variations observed. Vicente et al. (1985) observed an inhibitory effect of transfused vWF on the DDAVP-induced release of vWF in haemophilia, while t-PA-release was not affected. The blood group, which has an influence on basal FVIII/vWF level (Wahlberg et al. 1984), did not affect the rise in FVIII/vWF seen here in healthy volunteers. In patients with von Willebrand's disease Type I, too, the blood group had no effect on the increase in FVIII/vWF (Mörsdorf et al., in press). Thus, the results do not support the concept of an individually consistent (and determined) response to DDAVP.

The pharmacokinetics of DDAVP has been investigated in several previous studies. However, the doses used were insufficient to exert any haemato-

logical effects. Using a less specific assay technique, the half-life of DDAVP was found to range from 61 to 124 min (Edwards et al. 1973; Pullan et al. 1978; Sörensen et al. 1984). Recently, Harris et al. (1986) used a highly sensitive and more specific antibody for DDAVP and found a half-life of 162 to 216 min after i.n. administration. These findings are supported by our results. The data suggest that a further increase in dose, regardless of the route of administration, or a decrease in dose interval to less than 12 h cannot be recommended.

In conclusion, evidence has been obtained of the equivalence of the haematological response to and bioavailability of DDAVP after i.v. and s.c. dosing. The response to intranasal DDAVP in this study was poor. Recent developments in intranasal administration, however, make it seem likely that future delivery systems will be capable of inducing a maximal and reproducible stimulation of haemostasis, which would be equivalent to the high efficacy of parenteral dosing, as demonstrated here.

Addendum. After preparation of this manuscript two reports appeared on the pharmacokinetics of DDAVP; Lethagen et al., *Thromb Haemostas* 58: 1033-1036 (1987) and Mannucci et al., *Thromb Haemostas* 58: 1037-1039 (1987). The half-lives in those studies ranged from 2.2 h (normal subjects) to 4.4 h (haemophiliacs), as in our results. No correlation was found between the DDAVP concentration and the increase in FVIII.

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